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(54) Title: USE OF BREQUINAR AND DERIVATIVES IN CHRONIC REJECTION OF ALLOGRAFTS AND XENOTRANSPLANTATION			
(57) Abstract			
Analogues of brequinar, e.g., of formula (I), are found to be useful in the treatment and prevention of allograft chronic rejection and xenograft hyperacute, acute or chronic rejection.			

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Use of Brequinar and Derivatives in Chronic Rejection of Allografts and Xenotransplantation

The invention relates to a new use for quinoline derivatives in free form or in pharmaceutically acceptable salt form in the manufacture of a medicament for the treatment and/or prevention of chronic rejection of an allograft; or hyper-acute, acute or chronic rejection of a xenograft, in a mammalian recipient thereof, utilizing quinoline derivatives and salts thereof.

2-Carbocyclic and 2-heterocyclic quinoline carboxylic acids are described in US 5,523,408, incorporated by reference, as potent inhibitors of dihydroorotate dehydrogenase, the fourth enzyme in the de novo pyrimidine nucleotide biosynthesis pathway, and therefore have a unique mechanism of action (inhibition of dihydroorotate dehydrogenase) which is distinct from other available immunosuppressive agents. They are useful in the treatment and/or prevention of organ transplantation rejection, graft versus host disease, autoimmune diseases, and chronic inflammatory diseases in a mammal.

Phenylquinoline carboxylic acids and their derivatives are described as tumor inhibiting agents in US 4,680,299, incorporated by reference. US 4,968,701 and US 5,204,329, incorporated by reference, disclose that the compounds of US 4,680,299 have immunomodulating and anti-inflammatory activity, and therefore, alone or with other immunosuppressive agents, would be useful in the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and myasthenia gravis; as well as organ transplantation rejection in general and graft vs. host disease; and also as anti-inflammatory agents in the treatment of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

3-Phenyl-5,6-dihydrobenz[c]acridine-7-carboxylic acid compounds and derivatives thereof are described as tumor inhibiting agents in US 4,918,077 and US 5,002,954, incorporated by reference. US 5,135,934 and US 5,190,753 describe the use of these compounds as immunosuppressive or immunomodulatory agents for the treatment and/or prevention of organ transplantation rejection in general, graft versus host disease, autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, myasthenia gravis and systemic lupus erythematosus, psoriasis and other chronic inflammatory diseases.

Organ transplants of liver, kidney, lung and heart are now regularly performed as treatment for endstage organ disease. Because of the current shortage of human donors for transplantable allografts, attention has focused on the possibility of using xenografts (transplants between species) in transplantation. One of the major obstacles in transplanting successfully xenografts in humans is immunological, especially antibody mediated hyperacute or acute rejection.

A further obstacle in allo- and xenotransplantation is the chronic rejection, and thus organ transplantation is not yet a clinically viable solution to irreversible organ disease.

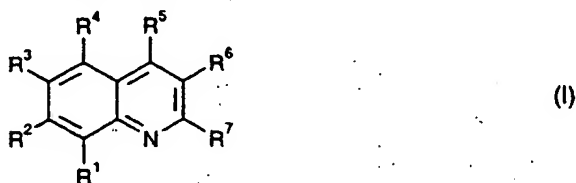
Chronic rejection, which manifests as progressive and irreversible graft dysfunction, is the leading cause of organ transplant loss, in some cases already after the first postoperative year. The clinical problem of chronic rejection is clear from transplantation survival times; about half of kidney allografts are lost within 5 years after transplantation, and a similar value is observed in patients with heart allografts.

Chronic rejection is considered as a multifactorial process in which not only the immune reaction towards the graft but also the response of the blood vessel walls in the grafted organ to injury ("response-to-injury" reaction) plays a role. The variant of chronic rejection with the worst prognosis is an arteriosclerosis-like alteration, also called transplant vasculopathy, graft vessel disease, graft arteriosclerosis, transplant coronary disease, etc. This vascular lesion is characterized by migration and proliferation of smooth muscle cells, probably under influence of growth factors that are amongst others synthesized by endothelial cells. This leads to intimal proliferation and thickening, smooth muscle cell hypertrophy repair, and finally to gradual luminal obliteration (vascular remodelling). It appears to progress also through repetitive endothelial injury induced amongst others by host antibody or antigen-antibody complexes; also so-called non-immunological factors like hypertension, hyperlipidemia, hypercholesterolemia etc. play a role.

Chronic rejection appears to be inexorable and uncontrollable because there is no known effective treatment or prevention modality. Thus, there continues to exist a need for a treatment effective in preventing, controlling or reversing manifestations of chronic graft vessel diseases.

It has now been found that quinoline derivatives of formula I as defined hereinafter are shown, unlike conventional immunosuppressants, e.g., Cyclosporin A or FK-506, to suppress antibody-mediated responses, as are characteristic in xenograft rejection, and are also indicated to prevent or combat chronic rejection in a transplanted organ.

Suitable quinoline derivatives are compounds of the formula I



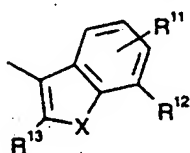
wherein

R^1 , R^2 , R^3 and R^4 are independently H, halogen, CF_3 , C_1 - C_4 alkyl, $S-CH_3$ or $S(O)_m-C_1$ - C_5 alkyl, at least two of R^1 , R^2 , R^3 and R^4 being H;

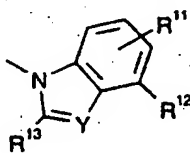
R^5 is $CO(O)H$ or $CO(O)C_2$ - C_4 alkylene- NR^8R^9 ;

R^6 is H or C_1 - C_3 alkyl or when R^7 is A^1 , A^2 or A^3 , also $-CN$, $-NR^8R^9$, $-OR^{10}$, $-SR^{10}$, $-NO_2$, $-CF_3$, $-OCF_3$ or $-SCF_3$;

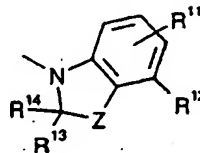
R^7 is a radical of formula A^1 , A^2 , A^3 or B



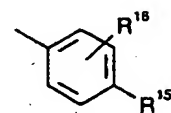
(A¹)



(A²)



(A³)



(B)

wherein

R^{11} is H, halogen, unsubstituted or halogen substituted C_1 - C_3 alkyl, $-NR^8R^9$, $-OC_1$ - C_3 alkyl or $-SC_1$ - C_3 alkyl;

R^{12} is aryl or heteroaryl which are optionally substituted by one or more substituents selected from H, halogen, unsubstituted or halogen substituted C_1 - C_3 alkyl, $-NR^8R^9$, $-OR^{10}$ and $-SR^{10}$;

R^{13} and R^{14} independently are H or C_1 - C_3 alkyl;

R^{15} is C_1 - C_{12} alkyl, C_6 cycloalkyl, C_4 heterocycloalkenyl, aryl, aralkyl, O-aryl, O-aralkyl,

$S(O)_m$ -aryl or $S(O)_m$ -aralkyl, wherein m is 0, 1 or 2 and aryl and aralkyl are optionally substi-

tuted by one or more substituents selected from H, halogen, unsubstituted or halogen substituted C₁-C₅alkyl, C₁-C₅alkoxy, NO₂ and OH;

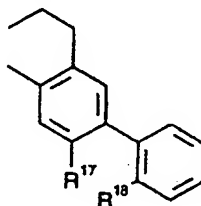
R¹⁶ is H, halogen, unsubstituted or halogen substituted C₁-C₅alkyl, C₁-C₅alkoxy, NO₂ and OH;

X is -N(R¹⁰)-, -O-, -S- or -CH=CH-;

Y is -N- or -C(R¹⁰)-; and

Z is -C(R⁸)(R⁹)-, wherein R⁸ and R⁹ independently are H or C₁-C₃alkyl; or

R⁶ and R⁷ together form a radical of formula C



(C)

wherein

R¹⁷ and R¹⁸ are H or taken together are S;

R⁸ and R⁹ are independently H or C₁-C₃alkyl; or R⁸ and R⁹ together form a C₄- or C₅alkylene which is optionally interrupted by -NH-, -N(CH₃)- or -O-;

R¹⁰ is H or C₁-C₃alkyl;

m is 0, 1 or 2;

with the following provisos for compounds wherein R⁷ is a radical of formula B

(a) R¹, R² and R³ cannot all be H;

(b) R¹⁵ cannot be C₆cycloalkyl when R⁵ is CO(O)(CH₂)₂-N(CH₃)₂, R³ is CH₂CH₃ or R² is Cl;

(c) when R¹⁵ is C₆cycloalkyl and R⁶ is H R³ must be Cl or F, but R³ and R¹ cannot both be Cl; and

(d) when R³ is CH₃, then R² cannot be Cl;

including their pharmaceutically acceptable salts and prodrug forms.

Halogen is to be understood as meaning a representative of the group consisting of fluorine, chlorine, bromine and iodine. Fluorine, chlorine and bromine are preferred, especially fluorine and chlorine.

Alkyl is intended to include both branched and straight chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms.

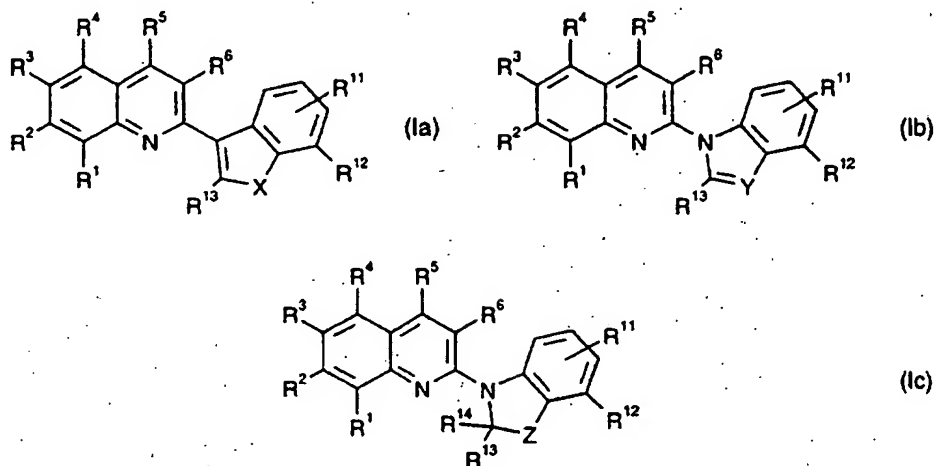
Cycloalkyl may contain preferably 5 to 8 and particularly preferably 5 or 6 ring carbon atoms.

For the purposes of the present invention, aryl or heteroaryl is a five- or six-membered ring or a bicycle consisting of two condensed six- or five-membered rings or one six-membered and one five-membered ring, and in the case of heteroaryl one or more C atoms may be replaced, independently of one another, by an atom selected from the group consisting of oxygen, nitrogen and sulfur. Examples are derived from benzene, naphthalene, indene, furan, pyrrole, pyrazole, imidazole, isoxazole, oxazole, furazan, thiadiazole, thiophene, thiazole, oxadiazole, triazole, indole, indazole, purine, benzimidazole, benzoxazole, benzothiazole, pyran, pyridine, pyridazine, triazine, pyrimidine, pyrazine, isoquinoline, cinnoline, phthalazine, quinoline, quinazoline, pteridine, benzotriazine or quinoxaline. Aryl is preferably naphthyl and phenyl. Phenyl is particularly preferred. Heteroaryl is preferably furanyl, pyridinyl and pyrimidinyl.

As used herein, "pharmaceutically acceptable salts and prodrugs" refer to derivatives of the disclosed compounds that are modified by making acid or base salts, or by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Examples include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids; acetate, formate and benzoate derivatives of alcohols and amines; and the like. Salts of carboxylic acid residues may include, but are not limited to, sodium, potassium, diethanolamine, N-methyl-D-glucamine, procaine, lysine, choline or tris-(hydroxymethyl)aminomethane.

Pharmaceutically acceptable salts of the compounds of this invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

In a preferred embodiment the compounds which can be used according to the invention have the formula Ia, Ib or Ic



wherein

R¹, R², R³, R⁴, R⁵, R⁶, R¹¹, R¹², R¹³, R¹⁴, X, Y and Z have the above meanings; including their pharmaceutically acceptable salts and prodrug forms.

More preferred are compounds of the formula Ia, Ib and Ic wherein R¹, R² and R⁴ are H; R³ is F or CF₃; R⁵ is CO(O)H; R⁶ is H or CH₃; R¹¹ is H; R¹² is phenyl which is optionally substituted by one or two substituents selected from H, CH₃, OCH₃, F and CF₃; R¹³ and R¹⁴ are H; X is -N(R¹⁰)- or -CH=CH-; Y is -N- or -C(R¹⁰)-; Z is -C(R⁸)(R⁹)-, wherein R⁸ and R⁹ independently are H or C₁-C₃alkyl; R¹⁰ is H or C₁-C₃alkyl; including their pharmaceutically acceptable salts and prodrug forms.

More preferred compounds according to the invention are compounds of formula Ia, Ib or Ic wherein R¹² is phenyl, 2-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl or 3-trifluoromethylphenyl.

Specifically preferred compounds useful in the present invention are compounds selected from the following:

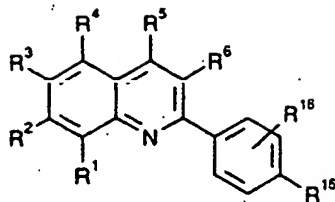
6-fluoro-3-methyl-2-(4-phenyl-1-indolinyl)-quinoline-4-carboxylic acid, sodium salt;

6-fluoro-2-[4-(2-fluorophenyl)-1-indolinyl]-3-methylquinoline-4-carboxylic acid, sodium salt;

6-fluoro-[4-(2-methoxyphenyl)-1-indolyl]-3-methylquinoline-4-carboxylic acid, sodium salt;
6-fluoro-3-methyl-2-[4-(2-methylphenyl)-1-indolyl]-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-[4-(3-methoxyphenyl)-1-indolyl]-3-methylquinoline-4-carboxylic acid, sodium salt;
6-fluoro-3-methyl-2-[4-(3-trifluoromethylphenyl)-1-indolyl]-quinoline-4-carboxylic acid,
sodium salt;
6-fluoro-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-2-[4-(2-methylphenyl)-1-indolyl]-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-2-[4-(3-trifluoromethylphenyl)-1-indolyl]-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, diethanolamine salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, N-methyl-D-glucamine
salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, procaine salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, lysine salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, choline salt;
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, tris-(hydroxymethyl)-
aminomethane salt;
6-fluoro-3-methyl-2-(5-phenyl-1-naphthyl)-quinoline-4-carboxylic acid, sodium salt;
6-fluoro-3-methyl-2-(7-phenyl-1-methyl-3-indolyl)-quinoline-4-carboxylic acid, sodium salt;
3-methyl-2-(7-phenyl-1-methyl-3-indolyl)-6-trifluoromethylquinoline-4-carboxylic acid, sodium
salt; and
6-fluoro-3-methyl-2-(6-fluoro-4-phenyl-1-benzimidazolyl)-quinoline-4-carboxylic acid.

Certain of the compounds of formula Ia, Ib and Ic may contain one or more asymmetric carbon atoms and may be isolated in optically active or racemic forms. All chiral, diastereomeric, and racemic forms are included in the present invention. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

In another preferred embodiment of the present invention the compounds which can be used according to the invention have the formula II



(II)

wherein

R¹, R², R³, R⁴, R⁵, R⁶, R¹⁵ and R¹⁶ have the above meanings;

including their pharmaceutically acceptable salts and prodrug forms;

with the following provisos

(a) R¹, R² and R³ cannot all be H;

(b) R¹⁵ cannot be C₆cycloalkyl when R⁵ is CO(O)(CH₂)₂-N(CH₃)₂, R³ is CH₂CH₃ or R² is Cl;

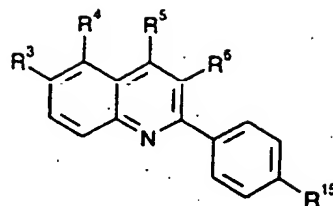
(c) when R¹⁵ is C₆cycloalkyl and R⁶ is H R³ must be Cl or F, but R³ and R¹ cannot both be Cl; and

(d) when R³ is CH₃, then R² cannot be Cl.

More preferred are those compounds of the formula II wherein R¹, R², R³ and R⁴ are independently H, F, Cl, Br, I, CH₃, CF₃, SCH₃ or CH₂CH₃, at least two of R¹, R², R³ and R⁴ being H; R⁵ is CO(O)H or CO(O)C₂-C₄alkylene-NR⁸R⁹; R⁶ is H, C₁-C₂alkyl or OC₁-C₃alkyl; R⁸ and R⁹ are independently H or C₁-C₃alkyl; R¹⁵ is C₁-C₁₂alkyl, C₆cycloalkyl, aryl, aralkyl, O-aryl, O-aralkyl, S(O)_m-aryl or S(O)_m-aralkyl, wherein m is 0, 1 or 2 and aryl and aralkyl are optionally substituted by one or more substituents selected from H, F, Cl, Br, C₁-C₅alkyl, CF₃, OCH₃, NO₂ and OH; R¹⁶ is H, F, Cl, Br, C₁-C₅alkyl, CF₃, OCH₃, NO₂ or OH; including their pharmaceutically acceptable salts and prodrug forms.

Most preferred are those compounds of the formula II wherein R¹ and R² are independently H or F, Cl, Br or I; R³ and R⁴ are independently H, F, Cl, Br, I, CH₃ or CF₃, at least two of R¹, R², R³ and R⁴ being H; R⁵ is CO(O)H, CO(O)K, CO(O)Na or CO(O)C₂-C₄alkylene-NR⁸R⁹; R⁶ is H or C₁-C₂alkyl; R⁸ and R⁹ are independently C₁-C₃alkyl; R¹⁵ is cyclohexyl, phenyl, phenyl substituted with one halogen, C₁-C₅alkyl, CF₃, phenoxy, phenoxy substituted with one halogen or C₁-C₅alkyl; and R¹⁶ is H.

Particularly preferred are compounds of the formula IIa



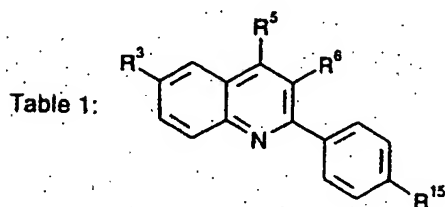
(IIa)

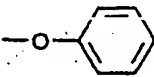

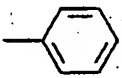
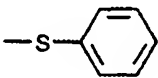
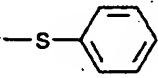
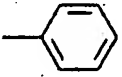
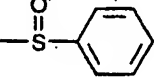
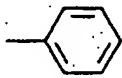
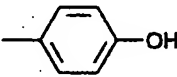
wherein R^3 and R^4 are independently H, halogen or CF_3 , provided that both R^3 and R^4 are not H; R^5 is $CO(O)H$, $CO(O)K$, $CO(O)Na$ or $CO(O)C_2-C_4$ alkylene- NR^8R^9 ; R^6 is H or C_1-C_3 alkyl; R^8 and R^9 are independently C_1-C_3 alkyl; R^{15} is cyclohexyl, phenyl, phenyl independently substituted with one or two substituents selected from halogen, C_1-C_5 alkyl and CF_3 , phenoxy, phenoxy substituted with one or two substituents selected from halogen, C_1-C_5 alkyl and CF_3 , provided that when R^{15} is phenyl or phenoxy, and R^4 is H, then R^3 cannot be Br; and that when R^{15} is cyclohexyl and R^6 is H, R^3 must be Cl or F.

Specifically preferred compounds useful in this invention are:

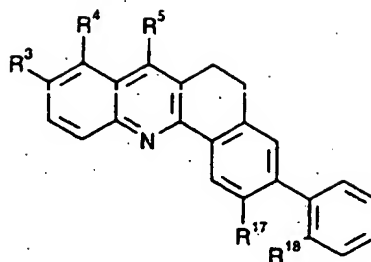
- 2-(1,1'-biphenyl-4-yl)-5-chloro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt;
- 2-(1,1'-biphenyl-4-yl)-5-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt;
- 6-fluoro-3-methyl-2-(4-phenoxyphenyl)-4-quinoline carboxylic acid, sodium or potassium salt;
- 2-(4'-bromo-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt;
- 2-(2'-fluoro-1,1'-biphenyl-4-yl)-6-fluoro-3-methyl-4-quinoline carboxylic acid, sodium or potassium salt.

Further compounds useful in the method of the invention are listed below in Table 1.



No.	R ³	R ⁵	R ⁶	R ¹⁵	m.p. [°C]
3	F	CO(O)Na	CH ₃		> 350
4	F	CO(O)Na	CH ₃		> 350
5	CH ₃	CO(O)Na	CH ₃		> 350
6	F	CO(O)Na	CH ₃	-S-CH(CH ₃) ₂	339-343
7	Cl	CO(O)Na	CH ₃		319-324
8	Cl	CO(O)K	CH ₃		310-325
9	F	CO(O)Na	H		> 360
10	F	CO(O)Na	CH ₃		251-260
11	F	CO(O)Na	OCH ₃		345-349
12	Cl	CO(O)Na	CH ₃		> 360

In still another preferred embodiment of the present invention the compounds which can be used according to the invention are of the formula III



(III)

wherein

R^3 , R^4 , R^5 , R^{17} and R^{18} have the above meanings; including their pharmaceutically acceptable salts and prodrug forms.

More preferred are compounds of formula III wherein R^3 and R^4 are independently H, F, Cl, Br, I, CH_3 , CH_2CH_3 , CF_3 or $S(O)_m-C_1-C_5$ alkyl; R^5 is $CO(O)H$ or $CO(O)C_2-C_4$ alkylene- NR^6R^9 ; R^6 and R^9 are independently H or C_1-C_3 alkyl; R^{17} and R^{18} are H or taken together are S; including their pharmaceutically acceptable salts and prodrug forms, in one embodiment, with the proviso that when R^5 is $CO(O)Na$ then R^3 is not F.

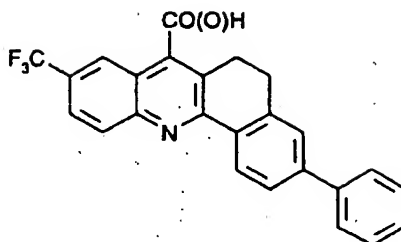
Most preferred compounds useful in the method of the present invention are those compounds of formula III wherein (a) R^5 is $CO(O)H$ or $CO(O)Na$; and/or (b) R^4 is H or Cl; and/or (c) R^3 is H, F, Cl or CF_3 .

Particularly preferred compounds useful in the method of the present invention are those compounds of formula III wherein (a) R^4 is H; and/or (b) R^3 is H, F or CF_3 .

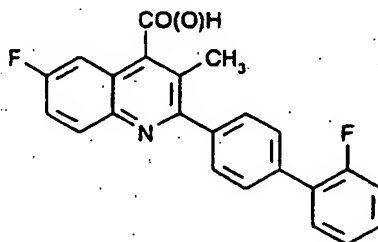
Specifically preferred compounds useful in the method of the present invention are:

- 5,6-dihydro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt;
- 5,6-dihydro-9-fluoro-3-phenylbenz[c]acridine-7-carboxylic acid, or a sodium salt;
- 6,7-dihydro-3-fluoro-[1]benzothieno[2',3':4,5]-benz[1,2-c]acridine-5-carboxylic acid, or a sodium salt;
- 6,7-dihydro-[1]-benzothieno[2',3':4,5]-benz-[1,2-c]acridine-5-carboxylic acid, or a sodium salt; and
- 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid; sodium salt.

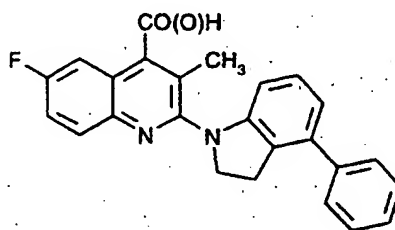
Most suitable compounds are



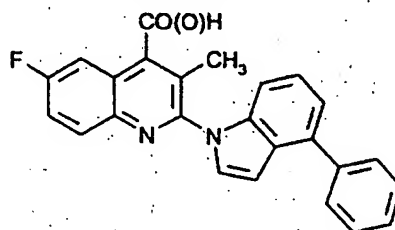
(i.e. 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid) in free or pharmaceutically acceptable salt form (e.g., sodium salt form); or



(i.e. 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid), or pharmaceutically acceptable salt form thereof (e.g., sodium salt form); or



(i.e. 6-fluoro-3-methyl-2-(4-phenyl-1-indoliny)-quinoline-4-carboxylic acid) or its pharmaceutically acceptable salt forms (e.g. sodium salt form); or



(i.e. 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid) or a pharmaceutically acceptable salt form (e.g. sodium salt form).

The compounds of formula Ia, Ib and Ic useful in this invention are described in and prepared by methods set forth in US 5,523,408, the disclosure, synthesis, and synthetic examples of which are hereby incorporated by reference.

The compounds of formula II useful in this invention are described in and prepared by methods set forth in US 4,680,299, the disclosure, synthesis and synthesis examples are hereby incorporated by reference. Further compounds are set forth in US 4,968,701 incorporated by reference herein.

The compounds of formula III useful in this invention are described in and prepared by methods set forth in US 4,918,077, US 5,002,954, US 5,135,934 and US 5,190,753, the disclosure, synthesis, and synthetic examples of which are hereby incorporated by reference.

According to the particular findings of the invention the compounds of formula I and their pharmaceutically acceptable salts and prodrug form are useful for the treatment and/or prevention of chronic rejection of an organ or tissue allograft; or hyper-acute, acute or chronic rejection of an organ or tissue xenograft, in a mammalian recipient thereof.

The invention thus provides:

1. A method of treating or preventing (i) chronic rejection of an allograft, or (ii) hyperacute, acute, or chronic rejection of a xenograft, comprising administering a therapeutically or prophylactically effective amount of a compound of formula I (in particular, 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or a pharmaceutically acceptable salt form thereof) (e.g., sodium salt form) to a subject in need thereof.
2. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula I (in particular, 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic

acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid in free acid or pharmaceutically acceptable salt form) (e.g., sodium salt form), together with a pharmaceutically acceptable diluent or carrier, for use in the treatment or prevention of (i) chronic rejection of an allograft, or (2) hyperacute, acute, or chronic rejection of a xenograft.

3. Use of a compound of formula I (in particular, 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid in free acid or pharmaceutically acceptable salt form) (e.g., sodium salt form), in the manufacture of a medicament for treating or preventing (i) chronic rejection of an allograft; or (ii) hyperacute, acute or chronic rejection of a xenograft.

4. Use of a compound of formula I (in particular, 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid in free acid or pharmaceutically acceptable salt form) (e.g., sodium salt form), for treating or preventing chronic rejection of an allograft of hyperacute, acute or chronic rejection of a xenograft.

Organs or tissues may be transplanted from a donor to a recipient of the same species (allograft) or different species (xenograft). Among such transplanted organs or tissues and given illustratively are heart, lung, combined heart-lung, trachea, liver, kidney, spleen, pancreatic (complete or partial, e.g. Langerhans islets), skin, bowel, or cornea or a combination of any of the foregoing.

Dosages of compounds of formula I required in practicing the present invention will vary depending on the compound of formula I employed, the host, the mode of administration, and the nature and severity of the condition to be treated. The compounds of formula I may be administered by conventional means, preferably orally, e.g., in the form of tablets or capsules, or parentally, e.g., in the form of injectable solutions or suspensions. In general, satisfactory results are obtained on oral administration at dosages of from about 0.1 to about 100 mg/kg/day, preferably from 1 to 20 mg/kg/day, e.g., 3 to 10 mg/kg/day, administered in

1, 2, 3, or 4 doses/day. Suitable daily dosages for oral administration to larger mammals, e.g., humans, are generally about 50 to 1500 mg, preferably in the order of from 200 to 800 mg.

The compounds can also be administered topically as an ointment, cream, gel, spray, inhaler, solution, aerosol, liposome, patch, etc.

Dosage forms used to administer the active ingredient usually contain suitable carriers, diluents, preservatives, or other excipients, as described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in the field.

The compounds of formula I for use in the treatment or prevention of xenograft rejection or chronic rejection may be administered alone or in combination with one or more other anti-inflammatory or immunosuppressive agents, e.g., as described above in connection with allograft rejection, for example in combination with cyclosporin A and analogs thereof, FK-506 and analogs thereof, rapamycin and analogs thereof, mycophenolic acid, mycophenolate mofetil, mizoribine, 15-deoxyspergualine, leflunomide, steroids, cyclophosphamide, azathioprene (AZA), or anti-lymphocyte antibodies or immunotoxins such as monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, or CD25; especially in combination with a T-cell suppressant, e.g., cyclosporin A or FK-506. Such combination therapy is further comprised within the scope of the invention, e.g., a method according to 1 above further comprising administration concomitantly or in sequence of a therapeutically or synergistically effective amount of such a second immunosuppressive or anti-inflammatory agent.

Utility of the compounds of formula I in treating diseases and conditions as hereinabove specified may be demonstrated in animal tests, for example in accordance with the methods hereinafter described.

A. In vivo heart xenotransplantation (hamster-to-rat)

The hamster-into-rat xenograft combination is a so-called difficult concordant combination. Rats do not have natural anti-hamster antibody in sufficient amounts to yield immediate hyperacute rejection as observed in concordant combinations; however, rejection in untreated recipients occurs within 3 to 4 days, by antibodies in combination with complement.

This is visualized in histology by destruction of blood vessels, exsudation and extravasation of erythrocytes, and influx by polymorphonuclear granulocytes; often there are signs of hemorrhage and thrombosis. Once this rejection has been overcome by effective inhibition of antibody synthesis or complement inactivation, a cellular rejection can emerge later on. This is visualized in histology by influx of mononuclear cells, including lymphocytes, lymphoblastoid cells, and macrophages, and destruction of the myocyte parenchyma. The inhibition of cellular rejection requires more immunosuppression than that of allografts. Congenitally athymic (rnu/rnu) rats lack a competent (thymus-dependent) cellular immune system and generally are unable to reject allografts. Such animals do reject a hamster xenograft within 3 to 4 days in a similar fashion as euthymic rats, indicative that (at least part of) anti-hamster antibody synthesis in rats occurs following a thymus-independent B-cell response. Such recipients are useful in hamster xenografting to evaluate rejection by thymus-independent antibody-mediated rejection.

The heart of a Syrian hamster is heterotopically transplanted in the abdomen of a male Lewis (RT1^l) rat, with anastomoses between the donor and recipient's aorta and the donor right pulmonary artery to the recipient's inferior vena cava. The graft is monitored daily by palpation of the abdomen. Rejection is concluded in case of cessation of heart beat. Animals are weighed weekly. In the present series of experiments, the endpoint is set to 28 days. Animals are subjected to autopsy; apart from the graft, weight and histology is assessed for thymus, spleen, liver, seminal vesicles and testes. Blood is taken and processed to serum for the determination of cytolytic anti-hamster erythrocyte antibody and hemolytic complement activity.

Compounds are dissolved in water and administered daily or twice daily (b.i.d.) orally in a volume of 2 ml/kg body weight. Administration of 5 to 30 mg/kg/day (e.g., 10 mg/kg/day) b.i.d. of a compound of formula I (in particular, 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz-[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indoliny)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, sodium salt) results in graft survival without signs of rejection or obvious pathology in both athymic and euthymic recipients through the endpoint of the experiment at 28 days.

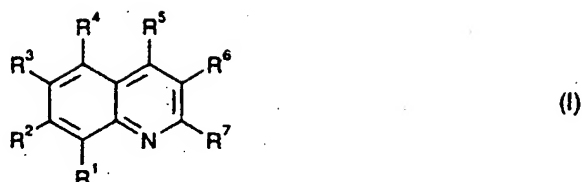
B. Chronic allograft rejection

The kidney of a male DA (RT1^b) rat is orthotopically transplanted into a male Lewis (RT1^k) recipient. In total 24 animals are transplanted. All animals are treated with cyclosporine A at 7.5 mg/kg/day per os for 14 days starting on the day of transplantation, to prevent acute cellular rejection. Contralateral nephrectomy is not performed. Each experimental group treated with a distinct dose of a compound of formula I or placebo comprises six animals.

Starting at day 53 to 64 after transplantation, the recipient animals are treated per os for another 69 to 72 days with a compound of formula I or receive placebo. At 14 days after transplantation animals are subjected to graft assessment by magnetic resonance imaging (MRI) with perfusion measurement of the kidneys (with comparison of the grafted kidney and the own contralateral kidney). This is repeated at days 53 to 64 after transplantation and at the end of the experiment. The animals are then autopsied. Rejection parameters such as MRI score, relative perfusion rate of the grafted kidney and histologic score of the kidney allograft for cellular rejection and vessel changes are determined and statistically analyzed. Administration of a compound of formula I, e.g. 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid, 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid, 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid, sodium salt, at a dose of 2.5 to 5 mg/kg in this rat kidney allograft model yields a reduction in above mentioned rejection parameters.

WHAT IS CLAIMED IS:

1. Use of a compound of formula I



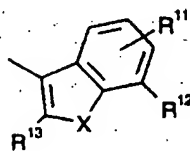
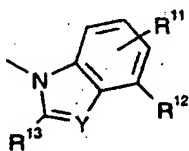
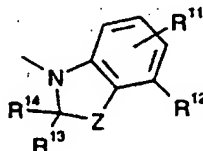
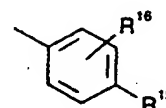
wherein

R^1 , R^2 , R^3 and R^4 are independently H, halogen, CF_3 , C_1 - C_4 alkyl, $S-CH_3$ or $S(O)_m-C_1$ - C_5 alkyl, at least two of R^1 , R^2 , R^3 and R^4 being H;

R^5 is $CO(O)H$ or $CO(O)C_2$ - C_4 alkylene- NR^8R^9 ;

R^6 is H or C_1 - C_3 alkyl or when R^7 is A^1 , A^2 or A^3 , also $-CN$, $-NR^8R^9$, $-OR^{10}$, $-SR^{10}$, $-NO_2$, $-CF_3$, $-OCF_3$ or $-SCF_3$;

R^7 is a radical of formula A^1 , A^2 , A^3 or B

(A¹)(A²)(A³)

(B)

wherein

R^{11} is H, halogen, unsubstituted or halogen substituted C_1 - C_3 alkyl, $-NR^8R^9$, $-OC_1$ - C_3 alkyl or $-SC_1$ - C_3 alkyl;

R^{12} is aryl or heteroaryl which are optionally substituted by one or more substituents selected from H, halogen, unsubstituted or halogen substituted C_1 - C_3 alkyl, $-NR^8R^9$, $-OR^{10}$ and $-SR^{10}$;

R^{13} and R^{14} independently are H or C_1 - C_3 alkyl;

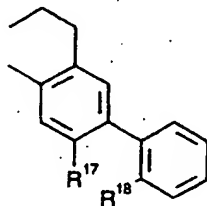
R^{15} is C_1 - C_{12} alkyl, C_6 cycloalkyl, C_4 heterocycloalkenyl, aryl, aralkyl, O-aryl, O-aralkyl, $S(O)_m$ -aryl or $S(O)_m$ -aralkyl, wherein m is 0, 1 or 2 and aryl and aralkyl are optionally substituted by one or more substituents selected from H, halogen, unsubstituted or halogen substituted C_1 - C_5 alkyl, C_1 - C_5 alkoxy, NO_2 and OH;

R^{16} is H, halogen, unsubstituted or halogen substituted C_1 - C_5 alkyl, C_1 - C_5 alkoxy, NO_2 and OH;

X is -N(R¹⁰)-, -O-, -S- or -CH=CH-;

Y is -N- or -C(R¹⁰)-; and

Z is -C(R⁶)(R⁷)-, wherein R⁶ and R⁷ independently are H or C₁-C₃alkyl; or R⁶ and R⁷ together form a radical of formula C



(C)

wherein

R¹⁷ and R¹⁸ are H or taken together are S;

R⁶ and R⁷ are independently H or C₁-C₃alkyl; or R⁶ and R⁷ together form a C₄- or C₅alkylene which is optionally interrupted by -NH-, -N(CH₃)- or -O-;

R¹⁰ is H or C₁-C₃alkyl;

m is 0, 1 or 2;

with the following provisos for compounds wherein R⁷ is a radical of formula B

(a) R¹, R² and R³ cannot all be H;

(b) R¹⁵ cannot be C₆cycloalkyl when R⁵ is CO(O)(CH₂)₂-N(CH₃)₂, R³ is CH₂CH₃ or R² is Cl;

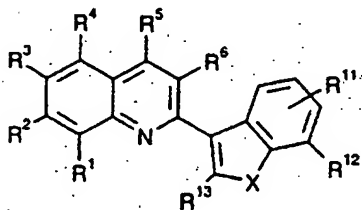
(c) when R¹⁵ is C₆cycloalkyl and R⁶ is H R³ must be Cl or F, but R³ and R¹ cannot both be Cl; and

(d) when R³ is CH₃, then R² cannot be Cl;

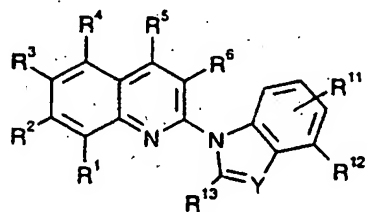
including their pharmaceutically acceptable salts and prodrug forms

in the manufacture of a medicament for treating or preventing (i) chronic rejection of an allograft or (ii) hyperacute, acute or chronic rejection of a xenograft.

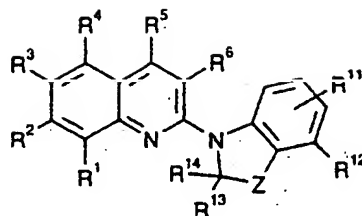
2. The use according to claim 1, wherein the compound has the formula Ia, Ib or Ic



(Ia)

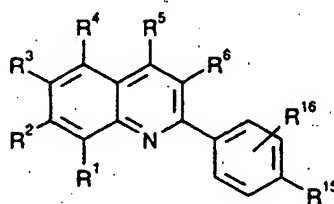


(Ib)



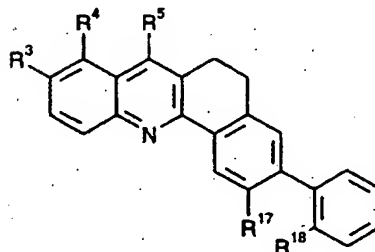
(Ic)

or the formula II



(II)

or the formula III



(III)

wherein

$R^1, R^2, R^3, R^4, R^5, R^6, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, X, Y$ and Z have the meanings according to claim 1.

3. Use of a compound of formula I according to claim 1, in free form or in pharmaceutically acceptable salt form, for treating or preventing chronic rejection of an allograft or hyperacute, acute or chronic rejection or a xenograft.

4. The use according to claim 1 or 3, wherein the compound is
 5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid,
 6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid,
 6-fluoro-3-methyl-2-(4-phenyl-1-indoliny)-quinoline-4-carboxylic acid or
 6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid

or a pharmaceutically acceptable salt form thereof.

5. The use according to claim 1 or 3, wherein the compound is in the sodium salt form.
6. Use of a compound of formula I according to claim 1, in the manufacture of a medicament for treating or preventing chronic graft rejection.
7. Use according to claim 1, wherein said medicament is administered concomitantly or in sequence with a second drug, said second drug being an immunosuppressive drug or an anti-inflammatory agent.
8. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula I according to claim 1 in free form or in pharmaceutically acceptable salt form together with a pharmaceutically acceptable diluent or carrier, for use in the treatment or prevention of (i) chronic rejection of an allograft, or (ii) hyperacute, acute, or chronic rejection of a xenograft.
9. The composition according to claim 8 wherein the compound is
5,6-dihydro-3-phenyl-9-trifluoromethyl-benz[c]acridine-7-carboxylic acid,
6-fluoro-2-(2'-fluoro-1,1'-biphenyl-4-yl)-3-methyl-4-quinoline carboxylic acid,
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid or
6-fluoro-3-methyl-2-(4-phenyl-1-indolyl)-quinoline-4-carboxylic acid in free acid or
pharmaceutically acceptable salt form.

INTERNATIONAL SEARCH REPORT

Intern. Application No. **PCT/EP 97/02401**

A. CLASSIFICATION OF SUBJECT MATTER
A 61 K 31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US, A, 5 578 609 (BATT et al.) 26 November 1996 (26.11.96), abstract; claims 2-7. --	1-3
X, P	US, A, 5 523 408 (BATT et al.) 04 June 1996 (04.06.96), abstract; claims 5-8. --	1-3
X	US, A, 5 204 329 (ACKERMAN et al.) 20 April 1993 (20.04.93), claims. --	1-3
X	US, A, 5 190 753 (BEHRENS et al.) 02 March 1993 (02.03.93), abstract; claims.	1-3

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 August 1997

Date of mailing of the international search report

09.09.97

Name and mailing address of the ISA

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Authorized officer

SCHNASS e.h.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 97/02401

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5 135 934 (BEHRENS et al.) 04 August 1992 (04.08.92), abstract; claims.	1-3
X	US, A, 4 968 701 (ACKERMAN et al.) 06 November 1990 (06.11.90), abstract; claims.	1-3
A	US, A, 5 002 954 (BEHRENS) 26 March 1991 (26.03.91), abstract; claims 11-20.	1-3
A	US, A, 4 918 077 (BEHRENS) 17 April 1990 (17.04.90), abstract; claims 11-20.	1-3

ANHANG

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

ANNEX

to the International Search
Report to the International Patent
Application No.

ANNEXE

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

PCT/EP 97/02401 SAE 160980

In diesem Anhang sind die Mitglieder
der Patentfamilien der in obenge-
nannten internationalen Recherchenbericht
angeführten Patentedokumente angegeben.
Diese Angaben dienen nur zur Unter-
richtung und erfolgen ohne Gewähr.

This Annex lists the patent family
members relating to the patent documents
cited in the above-mentioned inter-
national search report. The Office is
in no way liable for these particulars
which are given merely for the purpose
of information.

La présente annexe indique les
membres de la famille de brevets
relatifs aux documents de brevets cités
dans le rapport de recherche inter-
national visé ci-dessus. Les renseigne-
ments fournis sont donnés à titre indica-
tif et n'engagent pas la responsabilité
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In Recherchenbericht angeführtes Patentedokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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